

PUBLICATION

AUTHORS

John Duda, MD

Director

Parkinson's Disease Research,
Education and Clinical Center
Assistant Professor of Neurology
University of Pennsylvania
School of Medicine
Philadelphia, PA

Richard Robinson

Sherborn, MA

Diagnosing and Managing Parkinson's Disease: Practical Strategies for the Federal Healthcare Professional

COMPLIMENTARY CME/CE

The United States Department of Veterans Affairs (VA) treats an estimated 40,000 Veterans with Parkinson's disease (PD) yearly. This number, as well as the burden imposed on the VA system, is expected to increase due to the recent ruling that added PD to the list of presumed service-related disorders for Veterans who served in Vietnam. This policy shift is based on evidence suggesting that herbicide exposure may increase the risk of PD. Because patients may present at different stages of the disease and with varying levels of symptom severity, PD treatment must be highly individualized and requires consideration of multiple patient-specific factors. This educational activity is designed to help clinicians in the federal healthcare system become more confident and competent in the recognition, diagnosis, and optimal management of this complex disease.

ACTIVITY PLANNERS

Allison Gardner, PhD
Clinical Content Manager
Med-IQ
Baltimore, MD

Rebecca L. Julian, MS
Associate Managing Editor
Med-IQ
Baltimore, MD

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Series Overview/Statement of Need

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disease characterized by hallmark signs of bradykinesia, rigidity, tremor, and gait disturbances. It is superseded only by Alzheimer's disease as the most common neurodegenerative disorder. The prevalence of PD increases with age, and this is a growing concern as longer life expectancies in many populations, including in the United States (US), result in an increased need for healthcare resources.

The US Department of Veterans Affairs (VA) treats an estimated 40,000 Veterans with PD each year, and the disease imposes a relatively heavy burden on both Veterans and the VA. To improve care for this growing population of Veterans suffering from PD, the VA established six Parkinson's Disease Research, Education and Clinical Centers (PADRECCs) in 2001 to offer state-of-the-art treatment of PD and other movement disorders, as well as to provide education for both the professional community and patients.

The robust research efforts carried out by the federal government is especially important in light of the recent policy amendment that added PD to the list of diseases presumed to be service-related for Veterans who served in combat roles in Vietnam, based on evidence suggesting that Agent Orange exposure may increase the risk of PD. This development holds important implications for healthcare delivery systems in general, and the VA in particular; the likely influx of PD patients demands that federal practitioners are up-to-date on evidence-based strategies to recognize and manage this complex disease.


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Original Release Date: April 26, 2011
Expiration Date: April 25, 2012
Estimated Time to Complete This Activity: 1.0 hour

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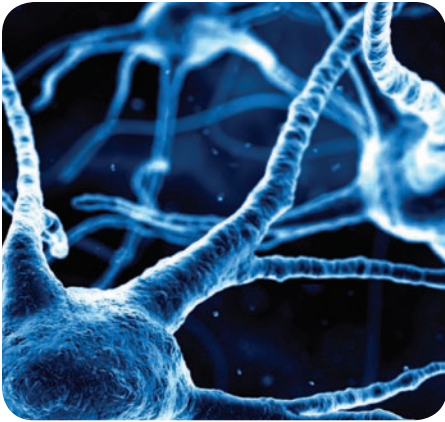
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Acknowledgment of Commercial Support

This activity is supported by an educational grant from Teva Pharmaceuticals.





Learning Objectives

Upon completion, participants should be able to:

- Recognize the impact of PD on healthcare systems and understand the ramifications of recent Federal regulation changes on PD care in the VA system
- List the common signs and symptoms associated with PD
- Describe the primary disorders and clinical features that should be considered and identified in the differential diagnosis of PD
- Summarize expert recommendations and recent clinical evidence regarding optimal treatment strategies in PD
- Identify challenges associated with non-motor and treatment-related symptoms in PD and integrate effective methods for screening, diagnosis, and treatment

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Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, is associated with a variety of motor and non-motor symptoms that together have a profound impact on a patient's quality of life. PD affects between 500,000 and 1,000,000 people in the United States (US), a figure expected to double by 2030, and approximately 40,000 new cases are diagnosed each year.^{1,3} Additionally, PD incidence increases with age; the typical age of onset is in the early 60s, but approximately 10% of cases are diagnosed before age 45.² Men are affected more often than women.³

Significant developments in the understanding of the causes and treatment of PD have occurred in the past decade, and the PD landscape is one of the fastest changing in neurology. Additionally, in August 2010, the Department of Veterans Affairs (VA) added PD to the list of diseases presumed to be service-related for Veterans who served in combat roles in Vietnam, based on evidence suggesting that herbicide exposure may increase the risk of PD.⁴ This new policy is expected to increase the number of PD patients seeking treatment at VA Medical Centers.

Parkinson's Disease Within the Department of Veterans Affairs System

An estimated 40,000 to 80,000 Veterans have been diagnosed with PD, and that number is expected to rise in the coming decades due to both an aging population and to effects of prior

exposure to neurotoxic chemicals among Veterans, particularly during the Vietnam War. Currently, the 10-year cost of PD treatment within the VA is estimated at \$3.5 billion, but this figure is also expected to increase as more Veterans seek PD care.⁴

PADRECCs

The VA has been proactive in developing resources to provide top-quality care for Veterans with PD. In 2001, the agency established six Centers of Excellence for the study and treatment of PD (Figure 1), known as Parkinson's Disease Research, Education and Clinical Centers (PADRECCs), which are located at the VA Medical Centers in:

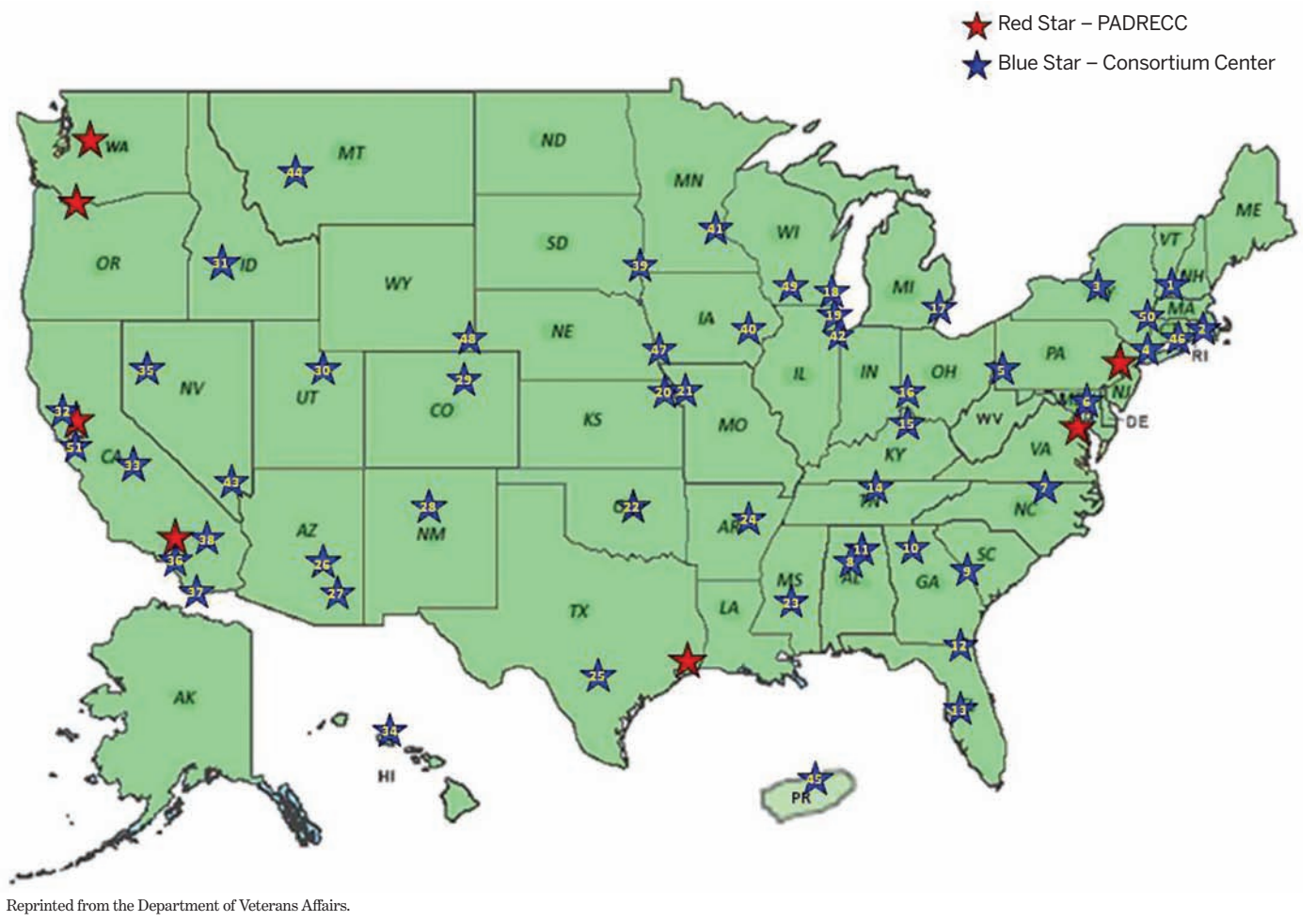
- Philadelphia
- Richmond
- Houston
- West Los Angeles
- San Francisco
- Portland/Seattle

PADRECCs have been leaders in research designed to improve the care of all patients with PD, including (but not limited to) Veterans.

Parkinson's Disease Consortium

The National VA Parkinson's Disease Consortium was established in 2003 to broaden the reach of PADRECCs and to improve and

FIGURE 1. National VA PD Consortium Center Network



Reprinted from the Department of Veterans Affairs.

modernize the care of PD across the VA healthcare system. The Consortium currently includes 50 centers, designated as Consortium Centers, where Veterans without access to a PADRECC can receive specialty PD care (www.parkinsons.va.gov/Consortium/NationalVAPDConsortiumNetworkandReferralList.asp).⁵ Consortium Centers offer movement-disorder specialists or neurologists familiar with PD treatment and are supported by PADRECCs through education, training, collaboration, and administrative assistance. Together, the PADRECCs and Consortium Centers create a hub-and-spoke system to maximize the availability of top-quality care for Veterans with PD.

VA centers may apply for Consortium Center designation. In addition, all clinicians employed by the VA who treat PD patients are encouraged to join the Consortium as individual members.⁶ Members gain access to valuable resources and educational materials, such as “The Monthly Transmitter,” which carries timely information on educational activities and reviews of recent research (apply for membership at www.parkinsons.va.gov/Consortium/MembershipandConsortiumCenterDesignationForm.asp).

Pathophysiology and Etiology

Epidemiology

PD is characterized by a progressive loss of dopaminergic and other types of neurons throughout the brain. Dopaminergic neurons projecting from the substantia nigra into the striatum are involved in complex control circuits that regulate aspects of movement.² Their degeneration leads to an imbalance of excitatory and inhibitory signaling within these circuits, changes that are believed to account for most of the motor aspects of the disease.

Recent pathologic studies have suggested that the disease process begins outside of the substantia nigra and starts long before the cardinal motor signs of PD develop.⁷ According to this model, the disease begins in the autonomic nervous system and olfactory regions, which may account for common early symptoms including constipation and the loss of olfaction.⁸ The disease then spreads upward, through the brainstem, and ultimately beyond it into the cortex, leading first to motor signs and then to cognitive decline in most patients. Degeneration affects many neurotransmitter systems beyond the dopamine system and accounts for many motor and non-motor symptoms of the disease, which are not levodopa-responsive, including:

- Gait abnormalities
- Autonomic symptoms
- Sleep dysfunction
- Neuropsychiatric features (including depression, anxiety, apathy, and cognitive impairment)

The growing conviction that PD pathogenesis begins years before diagnosis is further strengthened by the recent recognition that REM sleep behavior disorder (RBD) is a risk factor for PD.⁹⁻¹¹ More than one-half of patients diagnosed with RBD, which involves an absence of normal REM sleep atonia that causes patients to physically “act out” their dreams, are likely to develop

PD or a related neurodegenerative disease within 12 years, suggesting that RBD is an early manifestation of the same process that leads to clinical PD.¹¹

The significance of the model suggesting a long preclinical period in PD is 2-fold. First, factors that influence PD risk are likely to have an effect long before the disease manifests the cardinal motor symptoms, during the prodromal pre-motor phase of PD.¹² Second, it suggests that interrupting the disease process early, before the onset of motor symptoms, may be a realistic goal of future therapeutic interventions.

Genetic and Environmental Factors Associated With Parkinson's Disease

Although the etiology of most PD cases is unknown, both genetic and environmental factors are believed to play a role, with the relative contributions of the two varying among different patients. Age is the most important risk factor, with the incidence of disease rising steadily through middle into old age. Other identified risk factors include rural living, exposure to pesticides, and the consumption of well water, all of which suggest that environmental toxins are potential contributors to etiology.¹³ In contrast, a history of cigarette smoking is a protective factor and appears to be linked to duration, rather than intensity, of smoking.¹⁴ Caffeine intake is also associated with a lower PD risk.

Genetic Basis of Parkinson's Disease

Studies have shown that people with first-degree relatives with PD have a 3-fold increase in the risk of developing the disease; those with two or more first-degree relatives have a 10-fold greater risk.¹⁵ Multiple genes have been linked to PD, though none of them individually account for more than a small percentage of cases. The first abnormal protein linked to genetic PD was

α -synuclein, a neuronal protein involved in synaptic transmission.¹⁶ Although point mutations in the α -synuclein gene cause PD in only a few families worldwide, its discovery was fundamental to the understanding of PD pathogenesis because it was later demonstrated to be the principal component of Lewy bodies.¹⁷ Active, ongoing investigation seeks to clarify the roles of other important genes associated with PD, including^{18,19}:

- Glucocerebrosidase
- Leucine-rich repeat kinase 2
- Parkin

Recent genome-wide association studies have implicated a variety of new candidates that individually account for a relatively small number of PD cases, but collectively may account for a significant minority of genetic PD previously assumed to be sporadic.²⁰

Environmental Risk Factors

The role of environmental toxins in PD etiology has been the subject of intense research for several decades. Several chemicals, including the insecticide rotenone, can induce acute and specific damage to dopaminergic neurons in the substantia nigra, inducing a parkinsonian syndrome similar to PD; this suggests that

The growing conviction that PD pathogenesis begins years before diagnosis is further strengthened by the recent recognition that REM sleep behavior disorder (RBD) is a risk factor for PD.



one or more widely dispersed, but unidentified, toxins may contribute to disease risk in the general population.²¹

Some research suggests that a combination of genetic risk alleles and toxic exposure increase the risk of PD. For instance, one study found that the frequency of a specific allele for the detoxification enzyme glutathione transferase differed between PD patients and controls who had been exposed to pesticides, with a lower frequency of the protective allele in PD patients.²² In another study, a similar pattern was found with alleles for the blood-brain barrier transporter protein P-glycoprotein with the less functionally active alleles more common in PD patients who were professionally exposed to organochlorine insecticides.²³ Such findings support the complex interaction of genetic and environmental factors in PD pathogenesis.

Herbicides and Agent Orange

Herbicides have been implicated in PD and other diseases in both epidemiologic studies and animal models. Based on this association and the widespread exposure of servicemembers to herbicides used as defoliants during the Vietnam War, Congress passed Public Law 102-4, the Agent Orange Act of 1991, which resulted in a comprehensive and ongoing review of evidence regarding the health effects of Agent Orange and other herbicides that was conducted by the National Institutes of Medicine (IOM), a branch of the National Academy of Sciences.²⁴

Agent Orange (named because of the color of the drum it was stored in) was a 50:50 mixture of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic form of dioxin, was a contaminant introduced during the production of 2,4,5-T. More than 18 million gallons of herbicides (including Agent Orange and others) were sprayed across 3.6 million acres in Vietnam between 1961 and 1971.²⁵ The exact level of TCDD contamination is unknown and varied by batch

but is believed to have ranged from 0.05 ppm to 50 ppm. Likewise, servicemember exposure to herbicides varied. According to the IOM report, “reliable estimates of the magnitude and duration of such exposures are not possible in most cases, given the lack of contemporaneous chemical measurements and the lack of records of individual behaviors.”²⁵ According to the Agent Orange Act, Veterans who served in Vietnam who subsequently developed one of the diseases specified in the Act are presumed to have been exposed during their service to herbicides containing dioxin, “unless there is affirmative evidence to establish that the Veteran was not exposed to any such agent during that service.”²⁴

In their original analysis of the literature on herbicide exposure and risk of PD, the IOM concluded that evidence suggested a relationship between herbicide exposure and risk of PD, but found the studies lacking enough detail on level of exposure and specific agents to make a firm conclusion. More recent studies have suggested a link between PD risk and increased exposure to pesticides, including a modestly but significantly increased risk from exposure to 2,4,5-T and 2,4-D.^{26,27}

In addition to evaluating the epidemiologic evidence, the IOM reviewed laboratory data to determine whether the case for herbicide-related increased PD risk was “biologically plausible,” meaning that they were attempting to determine whether evidence of exposure in animal models and other systems supported the potential harm of exposure in humans. Although the evidence to date has been limited, the IOM concluded that, “the

preponderance of epidemiologic evidence now supports an association between herbicide exposure and PD and specifically implicates the chemicals of interest.”²⁵ As a result, in the 2008 update of the report, the committee changed its classification of the link

between exposure to herbicides and subsequent development of PD from “inadequate or insufficient evidence to determine an association” to “limited or suggestive evidence of an association.”

According to the Agent Orange Act, Veterans who served in Vietnam who subsequently developed one of the diseases specified in the Act are presumed to have been exposed during their service to herbicides containing dioxin.

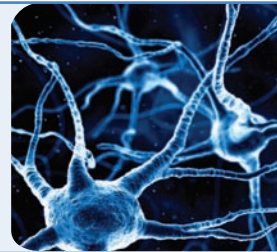


TABLE 1. Symptoms of Parkinson's Disease

MOTOR	SENSORY	NEUROPSYCHIATRIC	AUTONOMIC
Bradykinesia	Aching	Anxiety	Abdominal discomfort
Freezing	Anosmia	Cognitive decline	Constipation
Hypophonia	Pain	Dementia	Erectile dysfunction
Lower-extremity cramps	Restlessness	Depression	Orthostatic hypotension
Masked facies		Sleep disturbance	Sialorrhea
Micrographia			Urinary symptoms
Postural instability			
Rigidity			
Stooped, shuffling gait			
Tremor			

Derived from Weintraub D, Comella CL, Horn S. Parkinson's disease—part 1: pathophysiology, symptoms, burden, diagnosis, and assessment. *Am J Manag Care.* 2008;14(Suppl 2):S40-48 and Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry.* 2008;79(4):368-376.

On the basis of that change, on August 31, 2010, the VA issued its final rule adding PD to the list of diseases “subject to presumptive service connection based on herbicide exposure.”⁴

Clinical Features of Parkinson’s Disease

Although classified as a movement disorder, PD is characterized by a wide variety of both motor and non-motor symptoms (Table 1).

Motor Symptoms

The classic motor symptoms in PD can be remembered by considering PD a “TRAP,” characterized by²⁸:

- Tremor at rest
- Rigidity
- Akinesia or bradykinesia (halted or slowed movements)
- Postural instability

Symptoms usually begin unilaterally, and then progress to bilateral involvement. These symptoms are usually highly responsive to levodopa or other pharmacologic treatment, especially early in the disease.²

Tremor, however, may be less responsive than other symptoms in some cases.

Although action tremors may occur, tremors in PD are classically rest tremors; they occur at a frequency of 4 to 6 Hz and are often described as supination-pronation tremors (“pill-rolling” of the thumb and forefinger).^{2,28,29} Although it is often an early and visually prominent sign of PD, tremor is absent in as many as 30% of patients and is rarely the major cause of a patient’s disability.^{2,30}

Bradykinesia is typically the most debilitating symptom, affecting every aspect of activities of daily living. As a result of the slowed movements, patients may have difficulty rising from a chair, turning in bed, or dressing themselves.^{2,28} Rigidity, on the other hand, is often not reported by the patient but is revealed in the examination as resistance to passive movement in both flexors and extensors. Resistance may be either fluctuating (“cog-wheel”) or continuous (“lead-pipe”).²

Other prominent motor symptoms include postural instability and a stooped, shuffling gait, more often seen later in the disease.^{2,28} The development of postural instability often marks the transition to advanced PD because it increases the risk of falling, which, along with dementia, is a key predictor of placement in an assisted-living facility.²⁸ Postural instability is relatively resistant to levodopa treatment and is rarely improved by brain surgery.

Freezing is another late phenomenon in PD and is one of the most difficult symptoms to treat.²⁸ The patient, often without warning, finds him or herself unable to commence or continue movement, thus becoming frozen in place. Freezing often occurs when the patient is passing through a narrow opening such as a doorway, making a turn, or traversing a patterned surface such as a marked crosswalk. Freezing presents a high risk of falling. Sensory cues may be useful for some patients to break out of the frozen state, including²⁸:

- A marching command
- Music
- Visual prompt (ie, having the patient step over an object)

Many of the motor symptoms of PD can be thought of as the

result of diminished motor output, which may represent a mismatch between intended and actual motor effort. Thus, low voice volume, short stride length, loss of facial expression, and small handwriting are also characteristic of PD.²

Non-Motor Symptoms

The non-motor symptoms of PD may be as debilitating as the motor symptoms—or even more so. Nonetheless, patients may not report non-motor symptoms unless asked specifically about them, often thinking they are unconnected to PD. Non-motor symptoms may precede motor symptoms and may begin years or even decades before diagnosis based on the cardinal motor features of PD.¹² Many patients, for instance, report a long history of constipation and decreased sense of smell. Researchers have shown that using a simple smell test is an effective and low-cost screening tool for those at risk of developing PD, who might then be targeted for protective interventions if they become available.³¹

In most cases, pharmacologic agents that are effective in non-PD populations may be used to treat non-motor symptoms,

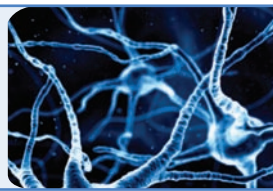
including anxiety, orthostatic hypotension, pain, and erectile dysfunction; however, there is a lack of evidence regarding the use of these treatments in PD.³² Constipation may be addressed

with bulk-forming laxatives and stool softeners, but prokinetics such as metoclopramide should be avoided as they have dopamine-blocking activities that worsen parkinsonism.³³

Depression. Reported rates of depression in PD patients vary widely, with estimates as high as 70%. The rate of depression in Veterans with PD was found to be lower than in the general population (18.5%), but it may be underdiagnosed in these patients.³⁴ Despite its importance in PD, little research has been done to determine the most effective agents for the treatment of depression in patients with PD. In 2006, a literature review-based Practice Parameter from the American Academy of Neurology indicated that only amitriptyline had been studied sufficiently to judge its effectiveness in PD; the evidence led the review panel to conclude it was “possibly effective in treating depression associated with PD,” but concerns were raised about the impact of cholinergic side effects on cognition.³⁵ A more recent short-term, head-to-head study compared the tricyclic nortriptyline with the controlled-release formulation of the selective serotonin reuptake inhibitor paroxetine in PD patients. Although both drugs were well tolerated, only nortriptyline was superior to placebo ($P < 0.002$); controlled-release paroxetine was not.³⁶ Additionally, pramipexole, prescribed for its motor effects, may have a direct antidepressant action in PD.³⁷

Dementia. Dementia occurs in up to 80% of PD patients, and the risk increases with age. Dementia at disease onset or shortly after diagnosis, however, is a red flag for an alternative diagnosis.² Acetylcholinesterase inhibitors, including galantamine, donepezil, or rivastigmine, are the treatments of choice for dementia in the context of PD.³⁵ Of these agents, however, rivastigmine is the only US Food and Drug Administration (FDA)-approved therapy for PD-associated dementia. In the current VA National Formulary, galantamine is considered first-line ther-

Non-motor symptoms may precede motor symptoms and may begin years or even decades before diagnosis based on the cardinal motor features of PD.



apy; donepezil, rivastigmine, and rivastigmine patch are non-formulary alternatives.²⁸ When treating dementia in patients with PD, it is reasonable to consider switching to an alternate agent in the event of unclear responsiveness or prohibitive side effects.

Diagnosis

“Parkinsonism” refers to the presentation of the classic motor features of PD—tremor at rest, bradykinesia, postural instability, and rigidity. Because parkinsonism is seen in a variety of disorders beyond PD, the clinical diagnosis of PD depends on the presence of three of the classic motor features, exclusion of other causes of parkinsonism (namely secondary parkinsonism or one of the atypical parkinsonian disorders), and response to dopaminergic-replacement therapy.²⁹

Secondary parkinsonism may be caused by dopamine-blocking drugs, toxic substances, infection, structural or vascular lesions, metabolic conditions, or trauma (Table 2).

The atypical parkinsonian disorders include parkinsonism as part of the clinical picture, but each has unique distinguishing features (Table 3). These features may become prominent only after parkinsonism develops, however, and early differentiation of PD from one of the atypical parkinsonian disorders can be a challenge even for an expert when such features are present in their mildest forms.^{2,29} Response to dopaminergic-replacement therapy is usually weaker in atypical parkinsonian disorders than for PD and lessens over time.

Essential tremor (ET) may occasionally be mistaken for early PD. ET is a slowly progressive disorder characterized by action (as opposed to rest) tremor and is usually bilateral at onset, rather than unilateral.²⁸ ET is not responsive to levodopa, but is often seen in the setting of a family history of tremor and can be improved with alcohol.

In 2010, the US FDA approved the use of ¹²³I-ioflupane as an adjunct to other diagnostic evaluations in distinguishing PD from ET. The agent is taken up by dopamine terminals in the brain, allowing a qualitative assessment of the integrity of the dopaminergic system when imaged using a single photon emission

TABLE 3. Atypical Parkinsonian Disorders

DISORDER	SUGGESTIVE FEATURES
Dementia with Lewy bodies	Dementia within 1 year of motor onset, visual hallucinations, cognitive fluctuations
Multiple system atrophy	Early and significant autonomic impairment, cerebellar dysfunction, long tract signs
Progressive supranuclear palsy	Supranuclear gaze palsy, early falls
Corticobasal degeneration	Profound asymmetry of parkinsonism, apraxia, cortical sensory impairment, alien limb phenomenon

Derived from Pahwa R, Lyons KE. Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. *Am J Manag Care.* 2010;16(4):S94-S99 and Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology.* 2009;72(Suppl 4):S1-S136.

computed tomography (SPECT) camera. The signal is normal in ET, but reduced in PD, secondary parkinsonism, and atypical parkinsonian disorders.³⁹ Although new in the US, ¹²³I-ioflupane has been in use since 2001 in Europe.

Treatment Considerations

PD treatment is complex and involves the use of nonpharmacologic treatments, a wide variety of pharmacologic agents, and—for some patients—brain surgery.

Treatment Planning

After a patient has been diagnosed with PD, questions arise regarding the proper timing and choice of treatment. Several different factors should be weighed in making these decisions. Currently, no agent has been conclusively shown to alter the course of the disease. Thus, the goals of PD treatment, which include both nonpharmacologic and pharmacologic approaches, are to reduce the impact of symptoms on both quality of life and the ability to carry out activities of daily living.⁴⁰ Important variables in treatment planning include:

- The patient's age
- Symptom severity
- Need or desire to continue working
- Concerns for the development of motor complications
- Preferences regarding treatment

To help clinicians evaluate patients and determine appropriate therapy, the VA PADRECC Clinical Care Committee developed an algorithm for initiating therapy in PD (Figure 2). However, this algorithm is intended to provide guidance and should not replace clinical judgement based on individualization of care and available clinical science.

Nonpharmacologic Treatments

Diet and exercise are as important for PD patients as for any group of older individuals. Because constipation is a common consequence of the disease, a high-fiber diet is important. It is also extremely important to maintain an exercise program that includes aerobic training, flexibility training, and strength training consistent with the patient's abilities. In addition to the recognized benefits for general health, such programs can help

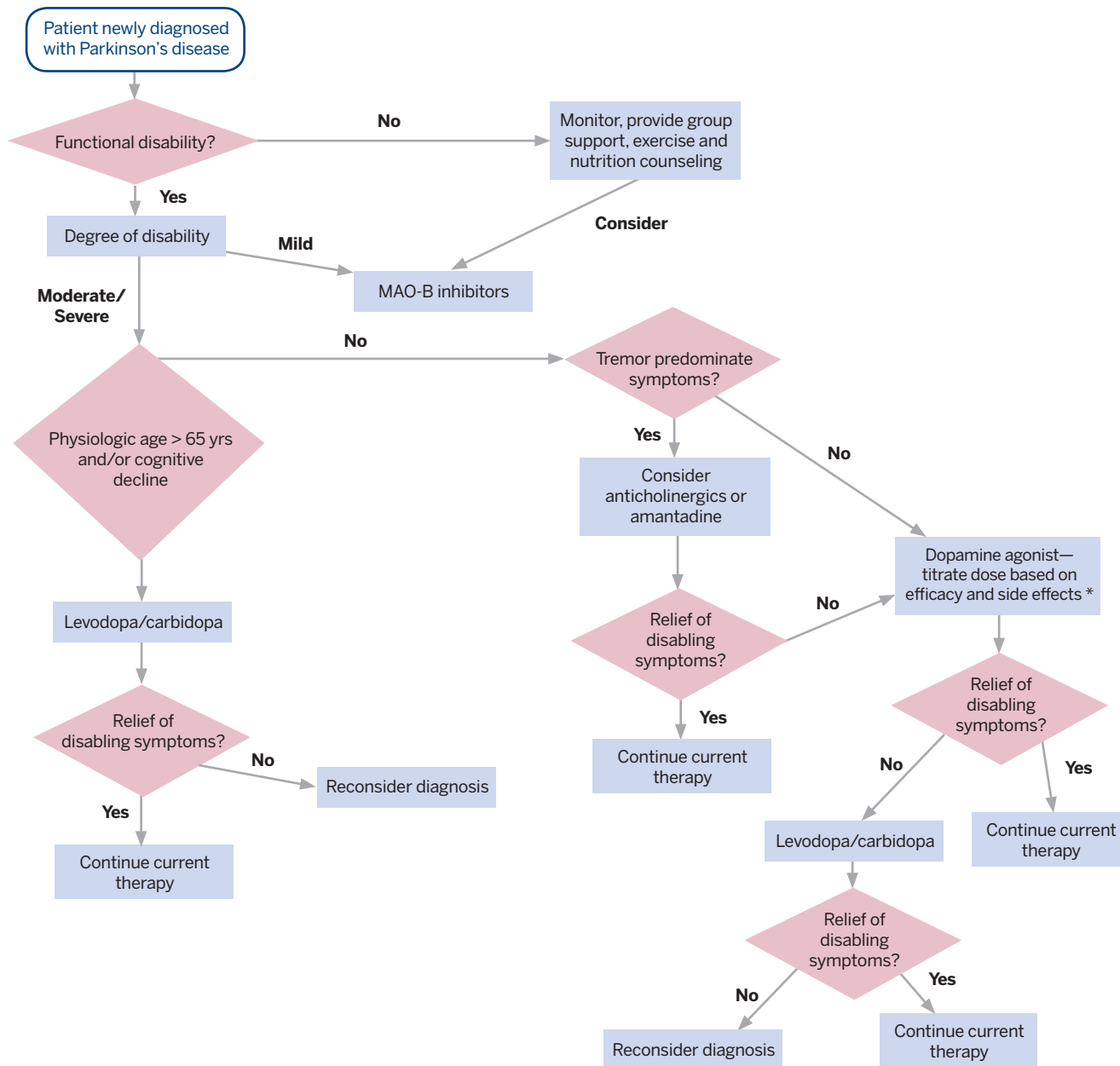
TABLE 2. Causes of Secondary Parkinsonism

CAUSE	EXAMPLE
Medications	Antipsychotics (eg, haloperidol, risperidone) Antiemetics/prokinetics (eg, metoclopramide, prochlorperazine)
Poisons	MPTP Carbon monoxide Manganese
Structural lesions	Stroke Hydrocephalus Trauma
Metabolic conditions	Wilson's disease
Infection	Encephalitis

Derived from Weintraub D, Comella CL, Horn S. Parkinson's disease—part 1: pathophysiology, symptoms, burden, diagnosis, and assessment. *Am J Manag Care.* 2008;14(Suppl 2):S40-48 and Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology.* 2009;72(Suppl 4):S1-S136.

FIGURE 2. Algorithm for the Early Treatment of PD

The movement disorder experts from the six PADRECCs developed the following algorithm to be used as a general **guideline**; it is not intended to interfere with clinical judgment or replace existing practice parameters.



*Assess for history of impulse control disorder-type behaviors (pathological gambling, eating, spending, sexual, etc) and consider using other agents if significant history and/or concerns exist; monitor for impulse control disorder-symptoms periodically during dopamine-agonist therapy. Developed by the VA PADRECC Clinical Care Committee. Subject to modification based on consideration of clinical science.

alleviate many symptoms of PD, including sleep disruption, constipation, mood disorders, and possibly cognitive impairment, while maintaining range of motion that can help in the prevention of falls.⁴¹ Walking, dancing, gardening, swimming, yoga, Tai Chi, and other forms of exercise all remain well within the abilities of most PD patients.

Pharmacologic Treatments

A variety of pharmacologic agents are available for the treatment of PD. Although none of these medications stop the pro-

gression of PD, the range of options allows physicians to individualize therapies according to patient-specific factors, as well as attempt to minimize adverse effects and optimize outcomes.

Amantadine. Amantadine provides mild antiparkinsonian activity and may be particularly useful in young patients with disabling tremor and as an adjunct to other treatments. It is also effective in many patients to reduce dyskinesia, a type of motor complication that develops with prolonged levodopa treatment.⁴⁰ Adverse effects include dry mouth, confusion, agitation, insom-

nia, constipation, and hallucinations, but most patients tolerate the drug well. Amantadine use, however, is limited by its association with cognitive effects and possible withdrawal symptoms upon discontinuation.

Anticholinergics. Anticholinergics such as trihexyphenidyl and benztropine may be beneficial early in the disease, especially for tremor.⁴⁰ Adverse effects, particularly cognitive effects, limit the use of anticholinergics later in the disease and in elderly patients.

COMT inhibitors. Entacapone and tolcapone are inhibitors of catechol-O-methyltransferase (COMT), which degrades levodopa in the periphery. COMT inhibitors are prescribed only in combination with levodopa. The primary goal of this approach is to increase the effectiveness of the levodopa dose and prolong the duration of response; in addition, the levodopa dose is sometimes reduced at the start of therapy to prevent dyskinesias.^{40,41} Tolcapone is somewhat more effective than entacapone, but increases the risk of liver toxicity and requires regular monitoring. (Note that tolcapone is not included in the VA National Formulary.)³⁸ Adverse effects of both agents include diarrhea, which occurs in about 10% of patients, often appears 6 to 12 weeks after beginning therapy, and may necessitate drug discontinuation. Patients should also be made aware of the propensity for entacapone to cause a harmless discoloration of the urine.⁴⁰

Dopamine agonists. Apomorphine, bromocriptine, pramipexole, and ropinirole are dopamine agonists (DAs), which mimic the action of dopamine in the brain. When used in early stage disease, these agents can delay the need for levodopa therapy and postpone the onset of levodopa-induced motor complications. In a meta-analysis of clinical studies in patients with early PD, DA therapy was superior in efficacy to placebo, but was associated with more frequent adverse effects. Compared with levodopa, DAs were inferior in efficacy, but were associated with fewer motor complications. Nuisance adverse effects, such as hallucinations and somnolence, were also more prevalent with DAs.⁴² DAs may also be used as adjunctive therapy with other antiparkinsonian agents. A clinical trial investigating the potential disease-modifying effect of DAs in PD is currently underway.⁴³ (Note that pramipexole is not included in the VA National Formulary.)³⁸

DAs have a longer duration of action than levodopa, making dosing somewhat easier, and they do not compete with amino acids for transport across the gut as levodopa does.^{40,44} However, they require complex titration schedules during therapy initiation. Adverse effects of DAs include the dopaminergic effects of nausea, orthostatic hypotension, somnolence, and hallucinosis.⁴⁰ In addition, impulse control disorders occur in up to 10% of patients taking a DA, often manifesting as pathologic gambling, compulsive shopping, binge eating, and hypersexuality.⁴⁵

Levodopa. Levodopa is the “gold standard” for the treatment of PD. It is converted to dopamine in the brain by dopa decarboxylase, thereby replacing endogenous dopamine lost to dopaminergic neuronal death and improving most of the motor symptoms and some of the non-motor symptoms of the disease.⁴⁰ It is administered with carbidopa to prevent the conversion of levodopa in the periphery. However, the therapeutic benefit of levodopa is limited by its propensity to induce motor fluctuations and dyskinesias, especially in younger patients.

Levodopa crosses the small intestine on the same carrier the body uses to absorb some amino acids.⁴⁴ Thus, it may be neces-

sary to take levodopa doses one hour before or after meals or with low-protein meals to avoid competition for transport, especially later in the disease course.⁴¹ Adverse effects are similar to those seen with DAs and include nausea, orthostatic hypotension, and somnolence. Levodopa, in combination with carbidopa, is available in three different formulations including standard release, extended release, and in combination with entacapone. In general, the standard-release levodopa formulation is the preparation of choice, often given 3 times a day (upon waking, before lunch, and before dinner).³⁸ (Note that combination carbidopa/levodopa/entacapone is not included in the VA National Formulary.)

MAO-B inhibitors. MAO-B inhibitors provide mild symptomatic relief in PD by preventing dopamine catabolism in the brain.⁴⁰ Two agents, selegiline and rasagiline, are both approved for adjunctive therapy in PD; rasagiline is also approved for early monotherapy. Rasagiline was recently added to the VA National Formulary in April 2011, but its use is restricted to movement-disorder practitioners or locally designated experts only.³⁸ MAO-B inhibitors are normally well tolerated at the doses used in PD, but adverse effects may include nausea, insomnia, and confusion.⁴⁰

Clinical investigation has focused on a disease-modifying effect of MAO-B inhibitors in early PD, based on preclinical work suggesting that it may protect dopamine neurons from cell death in experimental models. However, early experience in studies examining the neuroprotective effects of selegiline and levodopa revealed a need for a novel trial design to discern an agent’s effect on disease progression from short-term symptom improvement. More recent investigations of the neuroprotective properties of rasagiline employed a delayed-start design, in which participants were randomly assigned to receive initial treatment with rasagiline (early initiation) or placebo for one-half of the study period followed by rasagiline for the remainder (delayed start). Results from these studies suggest that the early initiation of treatment may be associated with less functional decline compared with a delayed start of treatment.^{46,47} However, there were discrepancies in outcomes between dosage arms of the largest study, with no statistically significant benefit seen at the highest dose.⁴⁷ This result tempers, but does not invalidate, conclusions regarding the potential disease-modifying properties of rasagiline and has sparked debate over the efficacy of the delayed-start design.⁴⁸ Although this model is not without its limitations, in the absence of a validated biomarker for disease progression, the delayed-start design is currently the best available strategy for clinical studies to investigate neuroprotective properties of PD medications.⁴⁹ It remains clear that additional large randomized clinical trials are needed.

Motor Complications

Motor complications can develop after several years of good response to therapy with dopaminergic agents. Delaying the start of levodopa therapy delays the onset of motor complications, but it does not alter their course or severity once they develop. The most common motor complications are⁴¹:

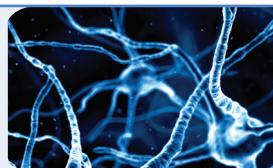
- Loss of benefit, or wearing-off, from a single dose of levodopa that may occur sooner than expected. Eventually, patients may experience motor fluctuations in which they repeatedly transition between being in the “on” state with good symptom control and the “off” state with poor symptom control. Treatment options include increasing the

dose, increasing the dosing frequency, or adding an adjunctive agent such as a COMT inhibitor, a DA, or an MAO-B inhibitor.

- Dyskinesias, or uncontrolled movements, most often occur when levodopa doses reach peak effectiveness. Treatment options include adding amantadine or a longer-acting agent such as a DA, as well as modifying the levodopa regimen by reducing the dose (with or without the addition of a COMT inhibitor), reducing the dose and increasing the dosing frequency, or switching to a sustained-release formulation.

The majority of patients with PD can be managed satisfactorily for several years with pharmacologic therapy, although with increasing levels of motor complications.⁴¹ Unfortunately, increasing the levodopa dose to control wearing-off can produce more dyskinesias, and reducing the levodopa dose to control dyskinesias can produce more wearing-off. Most patients choose an increase in dyskinesias, finding them to be less disabling than time spent in the “off” state.

The majority of patients with PD can be managed satisfactorily for several years with pharmacologic therapy, although with increasing levels of motor complications.



Surgical Treatment

The loss of dopaminergic neurons in the substantia nigra leads to an imbalance of the motor control circuits within the striatum. Although the system is complex and not entirely understood, one known consequence of this imbalance is excess output from several brain nuclei within these circuits. Surgery attempts to rebalance the circuits by reducing output from these nuclei. There are two important targets, the globus pallidus pars interna (GPi) and the subthalamic nucleus (STN), and two types of surgery, deep brain stimulation (DBS) and ablation.⁵⁰

In DBS, electrodes (leads) are implanted into the target site, usually bilaterally, and deliver high-frequency stimulation, which is thought to depolarize neurons within the field. The leads are attached to wires that run subcutaneously over the scalp and neck to a battery-powered, programmable pulse generator, which is implanted below the collarbone. Each lead has multiple

contacts that can be independently programmed, allowing the stimulation to be fine-tuned after surgery, a process that often requires the services of a specialist trained in DBS stimulator management to achieve an optimal response.⁵⁰ The rate of complications from surgery is highly variable. Infection, electrode fracture and migration, and intracranial hemorrhage occur in up to 19% of patients, with more experienced centers reporting the fewest complications.⁵⁰

DBS is the most common type of surgery currently performed, however ablation remains an option for patients who have an increased risk of infection, cannot return frequently for programming, or will not tolerate implanted hardware.⁵⁰ A recent large, double-blind, multicenter trial compared GPi with STN stimulation and found that each provided significant benefits in motor function.⁵¹

Surgery is an important treatment option for cognitively intact

patients with advanced PD who have developed disabling dyskinesias or motor fluctuations but still retain a good response to levodopa. Before patients undergo

surgery, however, they should be referred to a movement-disorder specialist to optimize medical therapy.⁵⁰ For appropriate patients, surgery has the potential to significantly improve quality of life by reducing motor fluctuations and dyskinesias.⁵²

Quality of Care in Parkinson's Disease

PD treatment is highly individualized in all cases, and care is often improved when overseen by a specialist. A PADRECC study of care delivery in more than 400 Veterans indicated that those seen by movement-disorder specialists were more likely to receive quality care than those seen by general neurologists. Similarly, general neurologists delivered better care than non-neurologists.⁵³

In 2010, the American Academy of Neurology issued recommendations outlining 10 quality care measures for patients with PD (Table 4).⁵⁴ Each measure defines the frequency of a clinical

TABLE 4. Quality Measures of Care for Patients With PD

QUALITY MEASURE	FREQUENCY
Annual PD diagnosis review	At least annually
Psychiatric disorders or disturbances assessment	At least annually
Cognitive impairment or dysfunction assessment	At least annually
Querying about symptoms of autonomic dysfunction	At least annually
Querying about sleep disturbances	At least annually
Querying about falls	Every visit
PD rehabilitative therapy options	At least annually
PD-related safety issues counseling	At least annually
Querying about PD medication–related motor complications	Every visit
PD medical and surgical treatment options reviewed	At least annually

PD = Parkinson's disease.

Derived from Cheng EM, Tonn S, Swain-Eng R, Factor SA, Weiner WJ, Bever CT Jr; American Academy of Neurology Parkinson Disease Measure Development Panel. Quality improvement in neurology: AAN Parkinson disease quality measures: report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. *Neurology*. 2010;75(22):2021-2027.

cal practice that a PD patient should receive to improve care. Regardless of the specialization of the clinician managing the PD patient, attention to these issues and ongoing evaluation and revision of the management plan is essential to deliver the best patient care.

Conclusion

The accurate diagnosis and appropriate management of PD is complex and requires an understanding of the full range of motor and non-motor symptoms, treatment options, and motor complications. Because patients may present at different stages of the disease and with varying levels of symptom severity, PD treatment must be highly individualized and requires the consideration of multiple patient-specific factors. Patients in the VA healthcare system are fortunate in that they have specialized resources, including PADRECCs or VA PD Consortium Centers. These resources should be utilized whenever possible to help ensure that patients receive the highest-quality, comprehensive care available to them.

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Phone: _____ Fax: _____ E-mail: _____

Type of practice: VA Medical Center Community-Based Outpatient Clinic Community Living Center
 VET Center Domiciliary Other: _____

Approximately how many patients do you see each week? _____

Of these patients, approximately what percentage have Parkinson's disease (PD)? _____ %

ACTIVITY EVALUATION

Rate the extent to which this CME activity met the following learning objectives:	Minimally		3	4	5	Completely		N/A
	1	2				6	7	
1. Recognize the impact of PD on healthcare systems and understand the ramifications of recent Federal regulation changes on PD care in the VA system	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. List the common signs and symptoms associated with PD	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Describe the primary disorders and clinical features that should be considered and identified in the differential diagnosis of PD	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Summarize expert recommendations and recent clinical evidence regarding optimal treatment strategies in PD	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Identify challenges associated with non-motor and treatment-related symptoms in PD and integrate effective methods for screening, diagnosis, and treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Rate the extent to which this CME activity:	Minimally		3	4	5	Completely		N/A
	1	2				6	7	
Met your expectations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Is applicable to your practice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Used appropriate teaching methods	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Provided current scientific evidence to support content	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Addressed barriers to optimal patient management	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Provided useful non-educational resources (eg, patient handouts, tools to assess practice, resources)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Addressed the following 6 core competencies:								
Patient care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medical knowledge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Interpersonal and communication skills	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Professionalism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Systems-based practice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Practice-based learning and improvement	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Needs Improvement			Average		Outstanding		
Compared to all other CME activities similar to this one that I have participated in over the past year, I would rate this program as:	1	2	3	4	5	6	7	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Did this activity provide fair and balanced content free from commercial bias? Yes No

(Commercial bias is defined as information presented that advocates a specific proprietary business product or service of a commercial interest.)

As a result of this learning experience, what will you do differently in the care of your patients? _____

How will you implement these changes? _____

Which of the following practice changes do you intend to implement as a result of participating in this learning experience?

- A. I will incorporate a new tool, such as the treatment algorithm, into my practice
 B. I will consider the latest evidence on pharmacologic treatment options when determining appropriate therapy
 C. I will routinely provide exercise and nutrition counseling to my PD patients
 D. I will assess my PD patients at least annually for psychiatric disorders and cognitive impairment
 E. I will refer patients to a PADRECC or VA PD Consortium Center for care when appropriate
 F. Other (please specify): _____
 G. None

Are there specific barriers to PD patient management that you feel better equipped to address as a result of this activity? If so, please list them.

Are there specific barriers to PD patient management that this activity did not address? If so, please list them.

I would like to see CME/CE activities on these topics: _____

Other comments (eg, what can we do to improve future CME/CE activities?): _____

ATTESTATION AND SIGNATURE REQUIRED TO RECEIVE CREDIT:

Physicians: I claim: _____ (maximum 1.0) AMA PRA Category 1 Credit™

Nurses: I claim _____ (maximum 1.0) contact hour for RNs, LPNs, LVNs, and NPs

Pharmacists: I claim _____ (maximum 1.0) contact hour/0.10 CEU

Signature: _____ **Date:** _____

NURSES: must provide license # to redeem credit _____

Post-Test

Name _____

(Please Print)

TE023NEU11 NL14-26-11 3/3

1. All of the following have been identified as possible risk factors for PD EXCEPT:

- A. Rural living
- B. Exposure to pesticides
- C. Consumption of well water
- D. History of cigarette smoking

2. Which of the following symptoms is/are usually the major cause(s) of disability in a patient with PD?

- A. Tremor
- B. Bradykinesia
- C. Rigidity
- D. All of the above

3. Non-motor symptoms may precede motor symptoms and may begin years before diagnosis based on the cardinal motor features of PD.

- A. True
- B. False

4. If a patient with PD has been experiencing levodopa-induced dyskinesia, which of the following would NOT be an appropriate adjunctive treatment?

- A. Amantadine
- B. An anticholinergic
- C. A COMT inhibitor
- D. A dopamine agonist

5. Which of the following variables should be considered in PD treatment planning?

- A. Concern about the development of motor complications
- B. Symptom severity
- C. Patient age
- D. All of the above

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